Smooth Muscle

Introduction

Smooth muscles are muscles. They contract. They use myosin and actin. They need calcium and ATP. That's about the extent of their similarities to skeletal muscles. Their orientation of thick and thin filaments is different, their use of calcium and ATP is different, their activities are different—everything is different. We've specifically chosen to teach smooth muscle separately from cardiac and separately from skeletal muscle because comparing them (teaching them together) only ensures confusion. We won't include a comparison table. There is overlap, and we'll use concepts from skeletal muscle contraction or make references to analogs. But think of smooth muscle as an entirely different topic altogether.

Smooth Muscle Cells and "Fibers"

Each smooth muscle cell is a fusiform elongated cell with only **one centrally located nucleus**. In order to be functional, there must be many of them, and they have to know how to act as one. Smooth muscles are connected to each other by **gap junctions**, sharing cytoplasm, ionic flow, and depolarizations, **effectively** forming a fiber. In addition to these electrical junctions that allow the communication of depolarization (action potentials), they're also connected through **mechanical junctions** called desmosomes. These allow strength to be applied to their bonds so when they contract, they don't just rip apart.

In a smooth muscle cell, **dense bodies** are connected to the cell membranes and are also where the **thin filaments** (actin) connect. Dense bodies are made of **α-actinin** and stabilize the smooth muscle actin filaments. Within the cell, dispersed seemingly sporadically throughout, are myosin filaments. When they contract, the myosin and actin slide past each other, the dense bodies get closer together, and the entire fiber is condensed. The dense bodies are smooth-muscle analogs to skeletal muscle's Z lines.

The cytoskeleton of smooth muscles is made of **intermediate filaments** with **desmin** as well as **vimentin** (but only when in vascular smooth muscle).

Smooth Muscle Actin and Myosin

While **actin does slide past myosin** in smooth muscle, much is different about the arrangement, compared to skeletal muscle. First, while smooth muscle cell's myosin is formed of **2 heavy and 4 light chains**, they do not connect tail to tail; rather they're staggered and opposite. Second, there's **no troponin** in smooth muscles, and the mechanism of contraction is entirely different. Third, there are **no sarcomeres**.

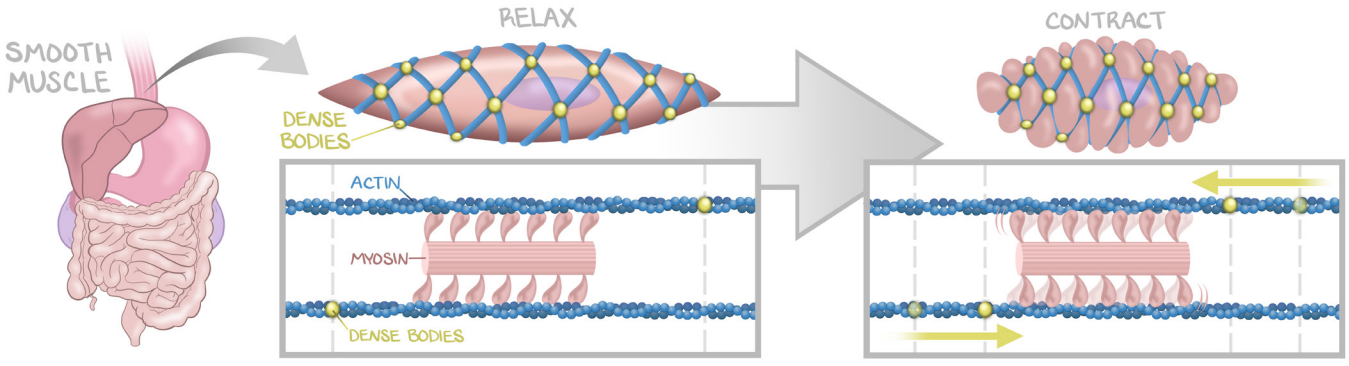

Figure 15.1: Smooth Muscle Actin and Myosin
Dense bodies anchor actin. Actin slides over myosin. Myosin heads are oriented in both directions, so that actin filaments slide in both directions over the myosin. This is similar to skeletal muscle (actin slides over myosin) but with a different purpose. Skeletal muscle slides two points closer together. Smooth muscle is contractile around a point.

A smooth muscle cell's **myosin heavy chain** forms in an antiparallel arrangement, such that the powerstroke goes in opposite directions. Rather than being tail-to-tail with a bare region between the two myosin chains, one myosin chain has its head down to the left, and the other up and to the right. The bare region for each myosin chain overlaps with heads of its partner. This arrangement allows for maximum sliding. There are no Z lines to collide with and no orientation necessary.

Smooth Muscle Contraction Mechanism

Despite word similarities between skeletal muscle and smooth muscle contraction the two should not be learned relative to each other. Learn smooth muscle contraction as an entirely separate and independent system.

Most of the calcium comes from the extracellular space and only a small amount comes from the sarcoplasmic reticulum**.** How calcium enters is discussed at the end of this lesson. Once in the cytoplasm, **four calciums** bind to a protein called **calmodulin** (**CaM**), activating it. The activated calcium-calmodulin complex binds to **myosin light-chain kinase (MLCK)**, activating the kinase activity. Without an active calcium-calmodulin complex, MLCK can't kinase. MLCK then goes to the myosin light chain, the regulatory chain on myosin heads, and "kinases" the regulatory light chain, **phosphorylating** it. Phosphorylation of the myosin light chain reveals the actin-binding site on myosin heads, allowing for the participation in cross-bridge cycling. In smooth muscle, actin is always ready, and it is myosin that has the inhibitory protein that must be removed to interact with actin.

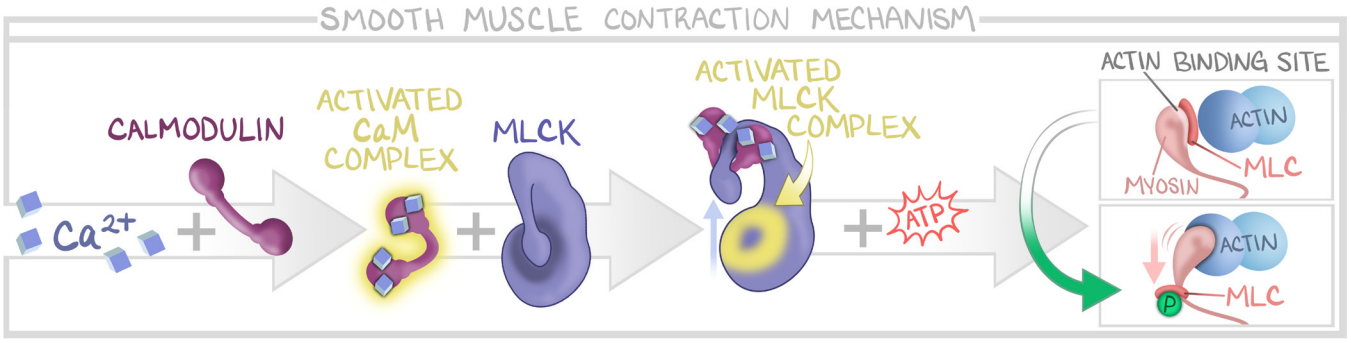

Figure 15.2: Smooth Muscle Excitation Contraction Mechanism
Calcium binds to calmodulin, activating it to activated CaM complex. CaM complex binds to and activates myosin light-chain kinase (MLCK). A kinase phosphorylates things. MLCK phosphorylates MLC. MLC is on the myosin heavy chain. When MLCK adds a phosphate onto MLC, it moves out of the way, off of the actin-binding domain of the myosin heavy chain, allowing the myosin and actin powerstroke to occur.

Sustained Contraction (Latch)

Smooth muscles control the lumen of many hollow organs and differ from one another primarily in what controls their contraction. They do not have a simple on-off system like skeletal muscle. Smooth muscles can be **tonic** or **phasic**. Sphincters are normally contracted, and open only momentarily to allow the passage of a bolus. This is tonic contraction—it stays contracted until it opens with relaxation. Skeletal muscle can't do that; it would just run out of ATP and fatigue.

The difference is in the cross-bridge cycling. In skeletal muscle, it's the binding of ATP that releases the myosin from actin. In smooth muscle, there has to be a myosin light chain phosphorylated by MLCK in order for association OR dissociation to happen. So, if the myosin happens to dephosphorylate while it's hooked up to the actin, ATP cannot reach its binding site to release myosin. In smooth muscle, **myosin remains in the position in which it was dephosphorylated.**

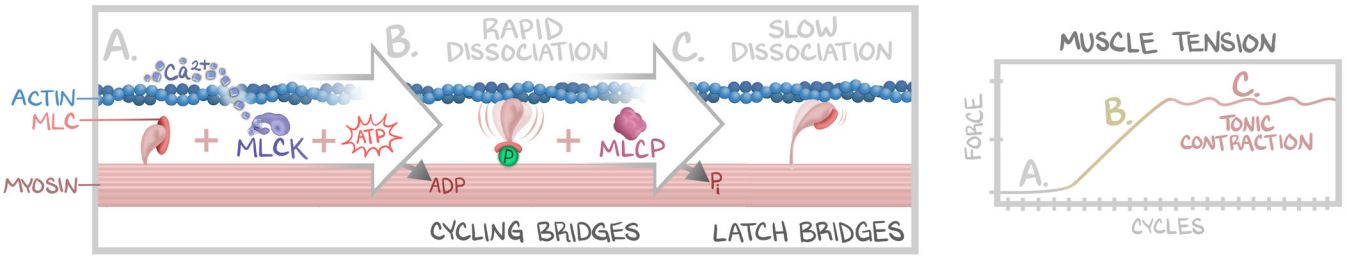

Figure 15.3: Latch Bridges and Powerstrokes
(a) Resting state. Myosin light chain is not phosphorylated. Myosin is not attached to actin. (b) Rapid dissociation. As long as myosin light chain is phosphorylated, myosin can undergo cycling of cross-bridges and powerstrokes. Dissociation of myosin from actin happens faster here, so that more powerstrokes can occur. (c) Slow dissociation, latch-bridge state. If dephosphorylated, MLC prevents the dissociation of myosin from actin if in the latched state. If dephosphorylated, MLC prevents the association of myosin to actin (resting state). Only smooth muscle has the dephosphorylated-but-not-dissociated latch-bridge state. This allows muscle tension to build through the rapid dissociation (b) until the force the smooth muscle wants is generated (c), where it leaves latch bridges for tonic contraction.

Relaxation

Calcium is restored to normal levels using the **Na^+-Ca^{2+} antiporter** of the plasma membrane and the **calcium-ATPase** found in both the sarcoplasmic reticulum membrane and the plasma membrane. This sequestering of calcium reduces the amount of calcium in the cytoplasm. Calcium-calmodulin complexes dissociate. Without the Ca^{2+}-CaM complexes, the feed-forward activation of MLCK is lost, so phosphorylation of myosin heads decreases. At the same time, a competing protein called **myosin phosphatase** (kinases add phosphates, phosphatases remove phosphates) takes over and myosin gets **dephosphorylated**.

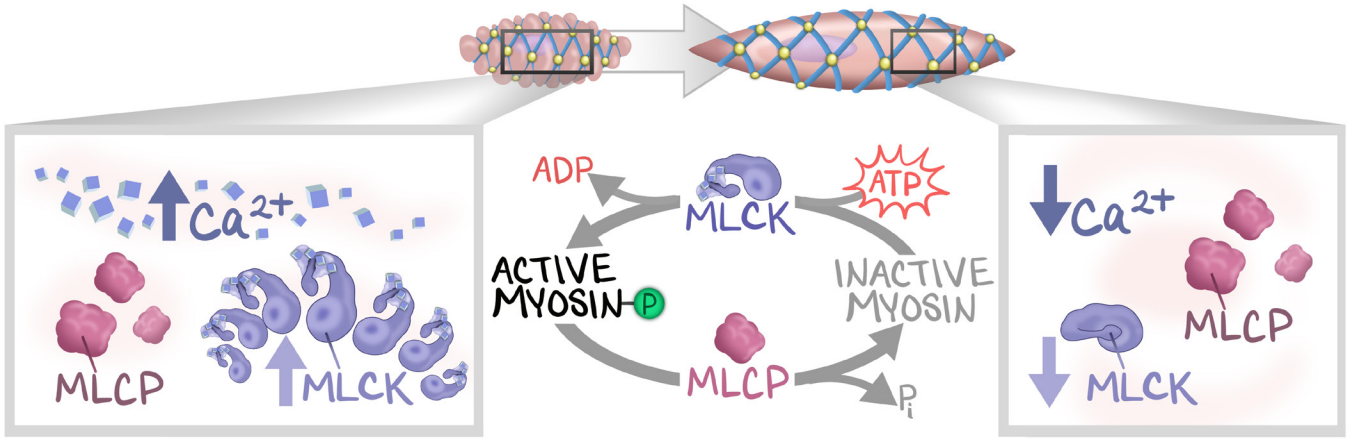

Figure 15.4: Relaxation and Calcium
Myosin light-chain phosphorylase (MLCP) has the same activity level regardless of calcium. Myosin light-chain kinase (MLCK) has increased activity with increased calcium, and decreased activity with decreased calcium. MLCK activates myosin and generates contractions. MLCP inactivates myosin, preventing the generation of new contractions. Eventually, all myosin dissociates from actin, even in the latch-bridge state. Varying calcium levels vary MLCK levels, which controls whether the cell will be in a generate-more-contraction state (calcium high, MLCK high, MLCK wins) or in a let's-not-change-anything state (calcium low, MLCK low, MLCP wins).

Where Calcium Comes from in Smooth Muscle

In skeletal muscle, the calcium stores come from one place, the sarcoplasmic reticulum, and from one mechanism—depolarization of the sarcolemma—leading to mechanical opening of a ryanodine channel. In smooth muscle, lots of things control calcium—a **depolarization is rarely needed** for smooth muscle to contract.

Calcium entry can be mediated from the extracellular matrix (the primary source of calcium in smooth muscle) by **voltage-gated calcium channels** (depolarization can cause a rise in calcium), by **stretch**-activated calcium channels (such as in the arterioles to maintain blood pressure), and by **ligand-gated second messenger cascades** such as the **G_q-IP_3-DAG** intracellular messenger system.

Regardless of how calcium gets into the cytoplasm, it binds CaM and activates MLCK, which phosphorylates the myosin light chain, thereby activating myosin.

Other intracellular mechanisms can further modulate CaM, MLCK, and myosin phosphatase, but that level of complexity is not appropriate here.

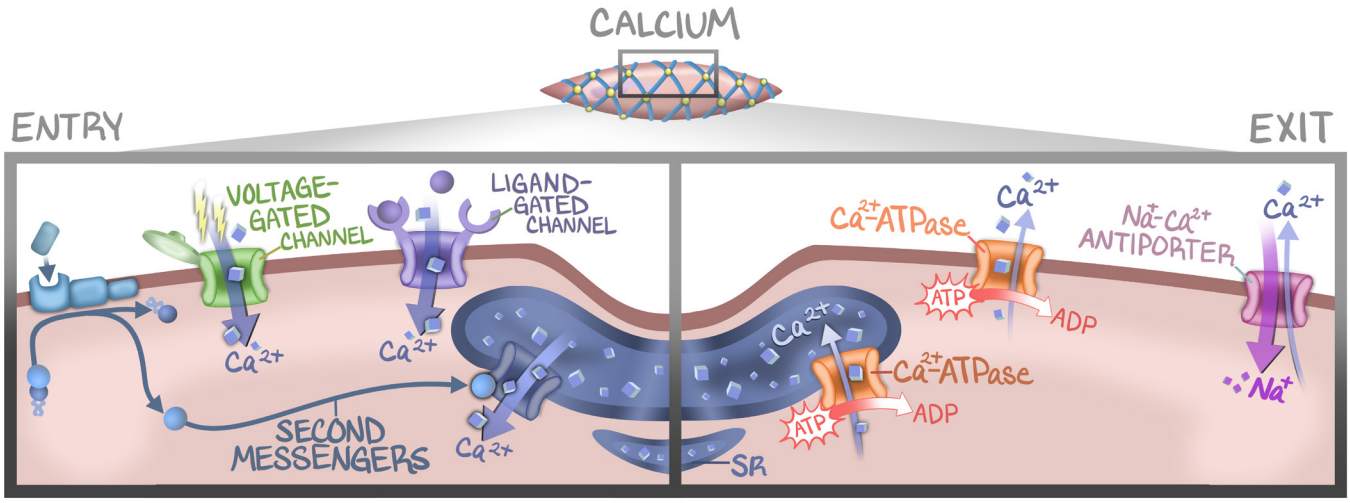

Figure 15.5: Where Calcium Comes from and Goes to in Smooth Muscle
The majority of calcium comes from the extracellular space. The sarcoplasmic reticulum has calcium channels, but smooth muscle does not rely on the rapid extrusion of calcium to generate a sudden massive contraction. There are many ways calcium gets into the cell—ligand-gated ion channels, voltage-gated ion channels, second messenger systems to the sarcoplasmic reticulum, stretch-activated ion channels. There are three main ways smooth muscle gets rid of calcium—Ca-ATPase, Na^+-Ca^{2+} antiporter, and the sarcoplasmic reticulum Ca^{2+}-ATPase.

Smooth Muscle Contraction Features

Slow cycling of cross-bridges. The cycling of myosin from actin to cocked and back to actin is very slow. Smooth muscle is not able to make many contractions, but the force of contractions remains stronger than in skeletal muscle for longer because the amount of time the myosin spends on the actin is so much longer. Smooth muscles do a sort of "rigor mortis"—they stay in the attached, powerstroked position, and do not dissociate.

This allows for a **sustained smooth muscle contraction** despite a **lower energy requirement.** Dissociation from the actin does involve ATP (just as in skeletal muscle), so there is an energy requirement. However, the cycling is slow and most of the time the myosin is attached to actin, so while there is an energy requirement, very **little ATP is used**. This matches with the **slow onset of contraction** and **slow onset of relaxation.** The smooth muscles aren't meant to run the organism away from a predator, but to sustain the position, or contraction, as in regulation of blood vessels. Because they're low-energy, slow to respond, and attain maximal force of contraction, smooth muscles can be used in very different ways than skeletal muscles.